Office Action Summary	Application No.	Applicant(s)	
	09/618,178	LINCOLN ET AL.	
	Examiner	Art Unit	
	STEPHANIE K. MUMMERT	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *16 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *75,76,78-82,85,86,91,92,94,95 and 116-118* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *75,76,78-82,85,86,91,92,94,95 and 116-118* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/16/08*.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *20081201* .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on October 16, 2008 has been entered.

Status of Claims

Claims 1-74, 77, 83-84, 87-90, 93, 96-115 have been canceled. Claims 116-118 are newly added. Claims 75-76, 78-82, 85-86, 91-92, 94-95, 116-118 are pending.

Claims 75-76, 78-82, 85-86, 91-92, 94-95, 116-118 are discussed in this Office action.

Applicant's arguments, see p. 11-18, filed October 16, 2008, with respect to the rejection(s) of claim(s) 75-76, 78-82, 85-86, 91-92, 94-95, 115 under Kimpton, Ledwina and Jean-Pierre have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of Nikiforov and Jean-Pierre.

All of the amendments and arguments have been thoroughly reviewed and considered but are not found persuasive for the reasons discussed below. Any rejection not reiterated in this

action has been withdrawn as being obviated by the amendment of the claims. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

This action is made NON-FINAL.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on October 16, 2008 was filed in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Claim Rejections - 35 USC § 112 - written description

Claims 75-76, 78-82, 85-86, 91-92, 94-95, 116-118 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification, describes the instant invention in very general terms, with regard to most of the steps of the method, but does not support the methods as claimed with sufficient detail to convey that the inventor(s) had possession of the claimed invention. First, the determination of the reaction value is described only generally, except for an embodiment comprising genetic bit analysis, which is described in some greater detail. Specifically, the specification states "in GBA, the approach is typically to hybridize a specific oligonucleotide to

the genetic material at the locus immediately adjacent to the nucleotide being interrogated. Next, DNA polymerase is applied in the presence of differentially labeled dideoxynucleoside.triphosphates. The read-out steps detect the presence of one or more of the labels which have become covalently attached to the 3' end of the oligonucleotide" (p. 4 of specification).

However, regarding the process of establishing a set of probability distributions, the specification does not provide sufficient guidance or detail regarding how these probability distributions are established. The specification states, "A distribution establishment arrangement establishes a set of probability distributions, including at least one distribution, associating hypothetical reaction values with corresponding probabilities for each genotype of interest at the locus" (p. 6 of specification). However, the specification does not clearly establish how the set of probability distributions are established, or how hypothetical reaction values are obtained. For example, regarding the distribution set, the specification states, "initial probability distributions are established for the G possible genotypes. For example in a random diploid population containing A tested alleles:

$G = (A) + (A- I) + ... + 1 = \frac{A(A+ I)}{2} (I)$"

and "The initial conditional probability for any hypothetical input datum (a point in M-space, denoted Xi) and genotype (denoted g) is defined as the prior probability of seeing the signal Xi assuming that g is the correct genotype of

25 that datum. That is:

Pr(signal Xi • Genotype = g),

where Xi = (x1/1 ... xM/1) and g • {i ... G}" (p. 13 of specification).

While equations are provided on p. 13, the specification is not clear about how these equations are used to establish probability distributions, how the hypothetical reaction values are established, or how the two are translated into conditional probability determinations. The specification, on this key point does not draw a clear connection between the specification and the claims. The specification does not provide clear support regarding each step of the method. Furthermore, the passage of the specification cited above was referred to with a "Probability Distribution" heading, yet refers both to distribution sets and conditional probability of a hypothetical data point. Without more details or raw data used in calculations which demonstrates how a data point is converted into a probability distribution or is modified by the distribution as required by steps C and D of claim 75, it not clear from a reading of the specification how to practice the invention. With only the end result of a "probability distribution" as provided in Figures 4 to 7, it is not possible to practice the invention without more information and therefore, there is not proper support in the specification.

Finally, reading the specification in light of the claims, it is unclear if the conditional probability measure is used to assign an entirely unknown genotype based on a data set or if the conditional probability is used to confirm a genotype that has been measured previously. This issue is raised primarily because the results of the first step of the method of claim 75, for example, leads to data that is organized in view of a previously measured genotype (see Figure 3). This is contrasted with the claimed result of claim 86, where a confidence score is calculated and associated with "the genotype in step (E), based on data from step (D)". The distinction between the end result of claim 75 and claim 86 is not clearly defined. Therefore, the

specification is unclear, regarding what is achieved as the final step of the method, particularly in claims 75, 116 and 118.

Therefore, due to the lack of specific support in the specification, the conclusion is reached that Applicant's have not demonstrated clear possession of the method as claimed at the time the invention was made.

Claim Rejections - 35 USC § 112 - enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 75-76, 78-82, 85-86, 91-92, 94-95, 116-118 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

Claims 75-76, 78-82, 85-86, 91-92, 94-95, 116-118 are drawn to a method of determining genotype comprising reacting material at a locus, collecting data, and determining the genotype of the subject at a given locus. The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

The claims encompass a method of determining genotype comprising reacting material at a locus, collecting data, and determining the genotype of the subject at a given locus. The claims also encompass multiple steps directed to establishing a set of probability distributions and applying the distributions to the reaction values.

Quantity of Experimentation

The quantity of experimentation in this area is large since there is significant variability in the steps as broadly claimed. The specification does not provide adequate support to effectively carry out the invention as claimed. Specifically, the claims refer to "establishing a distribution set of probability distributions" and "associating a hypothetical reaction value with corresponding probabilities of each genotype". However, the specification is entirely unclear as to how to achieve steps C) and D) of claim 75 and the related steps in other dependent and independent claims. First, the specification does not specifically teach how to obtain a reaction value, other than in most general terms. Next, the specification also does not teach how the distribution set of probability distributions are established or where the hypothetical reaction value(s) are obtained.

In order to recreate the instant invention and practice the method, without further detail or

instruction, would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

The unpredictability of the art and the state of the prior art

The state of the art at the time the invention was made appears to recognize the framework of applying conditional probability measurements to genotypes. In many instances in the prior art, these probabilities were associated with risk or with genotypes. For example, Ott et al. (PNAS, 1989, vol. 86, p. 4175-4178) teaches a computer simulation "for randomly generating genotypes at one or more marker loci, given observed phenotypes at loci linked among themselves and with the markers". Ott also teaches the "representation allows a recursive evaluation of the univariate probabilities that can be implemented in a surprisingly simple manner by carrying out successive 'risk calculations' with respect to marker genotypes given observed genotypes and marker genotypes already generated" (Abstract).

O'Connell et al. (Am. J. Hum. Genet., 1998, vol. 63, p. 259-266) note, "there is still a clear need for a rapid and efficient program to preprocess marker data, to determine if there are any typing errors and to assist the user in identifying them so that these errors can be resolved quickly. Ideally the program would be fast and efficient, would handle large data sets with perhaps hundreds of markers and thousands of individuals, would give detailed diagnostic information on the source of these errors, and would identify the individuals involved" (p. 259-260). O'Connell also teaches, "to provide researchers with such a tool, we have written a new program, PedCheck, for identification of marker-typing incompatibilities in pedigree data, that offers the capabilities described above and that also overcomes some of the difficulties and limitations present in existing packages" and "it processes one locus at a time, so that it is not limited by the number of markers it can handle; and it uses full genotype elimination to offer a

check that is more comprehensive than that of GAS" (p. 260).

There are numerous additional references in the state of the art at the time the invention was made and prior to the time of the invention that deal with genotype analysis, analyzing conditional probabilities associated with a genotype and confirmation of genotypes. These references establish a clear unpredictability in the art regarding the best manner in which to practice the steps of the instantly claimed method.

Working Examples

The specification has no working examples.

Guidance in the Specification.

The specification, describes the instant invention in very general terms, with regard to most of the steps of the method. First, the determination of the reaction value is described generally, except for an embodiment comprising genetic bit analysis, which is described in greater detail. Specifically, the specification states "in GBA, the approach is typically to hybridize a specific oligonucleotide to the genetic material at the locus immediately adjacent to the nucleotide being interrogated. Next, DNA polymerase is applied in the presence of differentially labelled dideoxynucleoside.triphosphates. The read-out steps detect the presence of one or more of the labels which have become covalently attached to the 3' end of the oligonucleotide" (p. 4 of specification).

Next, regarding the process of establishing a set of probability distributions, it is unclear how these probability distributions are established. The specification states, "A distribution establishment arrangement establishes a set of probability distributions, including at least one

distribution, associating hypothetical reaction values with corresponding probabilities for each genotype of interest at the locus" (p. 6 of specification). However, the specification does not clearly establish how the set of probability distributions are established, or how hypothetical reaction values are obtained. For example, regarding the distribution set, the specification states, "initial probability distributions are established for the G possible genotypes. For example in a random diploid population containing A tested alleles:

$G = (A) + (A- I) + ... + 1 = \frac{A(A+ I)}{2} (I)$"

and "The initial conditional probability for any hypothetical input datum (a point in M-space, denoted Xi) and genotype (denoted g) is defined as the prior probability of seeing the signal Xi assuming that g is the correct genotype of

25 that datum. That is:

Pr(signal Xi • Genotype = g),

where Xi = (x1/1 ... xM/1) and g • {i ... G}" (p. 13 of specification).

While equations are provided on p. 13, the specification is not clear about how these equations are used to establish probability distributions, how the hypothetical reaction values are established, or how the two are translated into conditional probability determinations. Some of the questions raised by the lack of clear connection between the specification and the claims as amended include: Is the probability equation cited above used for determining the probability distribution set, or is it used for establishing conditional probability for each genotype? Are the hypothetical Xi data points artibrarily established or are they based on the data set of step B? Furthermore, the passage of the specification cited above was referred to with a "Probability Distribution" heading, yet refers both to distribution sets and conditional probability of a

hypothetical data point. Without more details or raw data used in calculations which demonstrates how a data point is converted into a probability distribution or is modified by the distribution as required by steps C and D of claim 75, it not clear from a reading of the specification how to practice the invention. With only the end result of a "probability distribution" as provided in Figures 4 to 7, it is not possible to practice the invention without more information or clarification.

Finally, reading the specification in light of the claims, it is unclear if the conditional probability measure is used to assign an entirely unknown genotype based on a data set or if the conditional probability is used to confirm a genotype that has been measured previously. This issue is raised primarily because the results of the first step of the method of claim 75, for example, leads to data that is organized in view of a previously measured genotype (see Figure 3). This is contrasted with the claimed result of claim 86, where a confidence score is calculated and associated with "the genotype in step (E), based on data from step (D)". The distinction between the end result of claim 75 and claim 86 is not clearly defined. Therefore, the specification is unclear, regarding what is achieved as the final step of the method, particularly in claims 75, 116 and 118.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, the level of unpredictability and the lack of detailed explanation of how the invention is accomplished, lead to a conclusion of undue experimentation. Thus, given the broad claims in an art whose nature is identified as

unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the lack of a working example balanced only against the high skill level in the art, it is concluded that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Claim Rejections - 35 USC § 112 – 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 75 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are:

Claim 75 is directed to a method of determining a genotype. However, the claim is directed to only reacting the material at a first locus to produce a first reaction value. A genotype comprises results from two alleles at a locus. The claim is missing a step of determining a reaction value corresponding to the second allele at a locus and therefore does not achieve the end result of establishing a genotype at a locus and instead, at most, determines the sequence of a specific allele at a locus.

Priority

Applicant's claim of priority back to application 08/173,173, 07/775,786 and 07/664,837 is noted. The examiner was unable to determine whether these applications provide support for

the entirety of the current claims and therefore the claims are given the effective date of the immediate parent 09/088,820, which provides express support (except for claim 50, as detailed below).

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 75-76, 78-82, 85, 86, 91-93, 95, 96-98, 102, 106-109 and112-115 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nikiforov et al. (Nucleic Acids Research, 1994, vol. 22, no. 20, p. 4167-4175) in view of JeanPierre (Ann. Hum. Genet. (1992) 56:325-330).

With regard to claim 75, Nikiforov teaches a method of determining the genotype at a locus within genetic material obtained by PCR amplification from a subject (page 14) comprising:

a) reacting the material at the locus to produce a first reaction value indicative of the presence of a given allele at the locus, wherein the first reaction value is the intensity of an allele-specific quantitative signal (Figure 1, where the material at a locus is reacted to produce a first reaction value indicative of the presence of an allele at a locus),

b) forming a data set including the first reaction value (Figure 1, where the material at a locus is reacted to product a first reaction value indicative of the presence of an allele at a locus; Figure 2, where a data set is provided where alleles are detected by a colorimetric signal),

e) determining the genotype of said subject based on the data obtained from step D wherein each allele is a single specific nucleotide (Figure 1, where the material at a locus is reacted to product a first reaction value indicative of the presence of an allele at a locus; Figure 2, where a data set is provided where alleles are detected by a colorimetric signal).

With regard to claim 78, Nikiforov teaches an embodiment of claim 76, further comprising:

(i) reacting the material at the locus to produce a second reaction value (Figure 1, where the material at a locus is reacted to produce a first and second reaction value indicative of the presence of both alleles at a heterozygous locus).

With regard to claim 81, Nikiforov teaches an embodiment of claim 80, of determining the genotype at a locus within genetic material obtained from each of a plurality of samples, the method further comprising:

(i) performing step (A) with respect to the locus of material obtained from each sample; and

(ii) in step (B), including in the data set reaction values obtained from each sample (Figure 1, where the material at a locus is reacted to produce a first and second reaction value indicative of the presence of both alleles at a heterozygous locus).

With regard to claim 82, Nikiforov teaches an embodiment of claim 80, of determining the genotype of selected loci within genetic material obtained from a sample, the method further comprising:

(i) performing step (A) at each of the selected loci (Figure 1, where the material at a locus is reacted to produce a first and second reaction value indicative of the presence of both alleles at a heterozygous locus); and

(ii) in step (B), including in the data set reaction values obtained from each of the selected loci (Figure 2, where a data set is provided where alleles are detected by a colorimetric signal).

With regard to claim 91, Nikiforov teaches an embodiment of claim 78, wherein step (B) includes the step of including in the data set reaction values from prior tests at the locus obtained under comparable conditions (Figure 3, where the measured results include prior tests and synthetic oligonucleotides as controls).

With regard to claim 92, Nikiforov teaches an embodiment of claim 82, wherein the loci are selected on the basis of their ability to discriminate among subjects (Abstract, where Genetic Bit Analysis is "used on a large scale for the parentage verification of thoroughbred horses using a predetermined set of 26 diallelic polymorphisms in the equine genome).

With regard to claim 94, Nikiforov teaches an embodiment of claim 75, wherein step (A) includes the step of assaying for the given allele using genetic bit analysis, allele-specific

hybridization, or allele-specific amplification, including such amplification by a polymerase chain reaction or a ligase chain reaction (Figure 1, where the single nucleotide genotyping is accomplished by genetic bit analysis; p. 4170, where DNA typing by genetic bit analysis is described).

With regard to claim 95, Nikiforov teaches an embodiment of claim 82, wherein the loci are proximal to one another, so that the set of genotypes so produced may indicate a sequence of nucleotides associated with the genetic material (Figure 1, 2 and Table 1, where a variety of loci are analyzed and may be proximal to one another).

With regard to claim 116 and 118, Nikiforov teaches a method of determining the genotype of a subject at a locus within genetic material obtained from a biological sample from the subject, the method comprising:

A. reacting the material at the locus to produce a first optical signal indicative of the presence of a first allele at the locus, wherein the first allele is a single specific nucleotide;

B. reacting the material at the locus to produce a second optical signal indicative of the presence of a second allele at the locus, wherein the second allele is a single specific nucleotide (Figure 1, where the material at a locus is reacted to produce a first and second reaction value indicative of the presence of both alleles at a heterozygous locus).

With regard to claim 117, Nikiforov teaches an embodiment of claim 116 wherein step A includes the step of hybridizing a first oligonucleotide probe to the genetic material at the locus and step B includes the step of hybridizing a second oligonucleotide probe to the genetic material at the locus, wherein the first and second oligonucleotide probes are specific for the first and second alleles, respectively, at the locus (Figure 1, where a first and second oligonucleotide

probe are hybridized with the genetic material, which are specific for the first and second alleles, respectively).

Regarding claim 75-76, 78-80, 85, 91-92, Nikiforov does not teach establishing a distribution set or establishing conditional probability of a genotype at a locus. Jean-Pierre teaches analysis of probabilities of possible genotypes derived from conditional probabilities (Abstract).

With regard to claim 75, 80, 118, Jean-Pierre teaches an embodiment, comprising c) establishing a distribution set of probability distributions, including at least one distribution, associating hypothetical reaction value intensities with corresponding probabilities for each genotype of interest at the locus (p. 328, Table 1, where probability distributions for genotype are established);

d) applying the first reaction value to each pertinent probability distribution to determine a measure of the conditional probability of each genotype of interest at the locus, wherein the conditional probability is a measure of the likelihood of the genotype given the first reaction value (p. 328, where conditional probabilities of the genotypes were also calculated).

With regard to claim 76, Jean-Pierre teaches an embodiment of claim 75, wherein the distribution set includes a plurality of probability distributions for a corresponding plurality of genotypes of interest (p. 328, Table 1, where probability distributions for genotype are established).

With regard to claim 75-76, 78-80, 85, 91-92, Jean-Pierre teaches an embodiment comprising:

(ii) determine the probability of each genotype at the locus (p. 328, Table 1, where probability distributions for genotype are established);
(iii) applying the first and second reaction values to each pertinent distribution and determine a measure of the conditional probability of each genotype at the locus (p. 328, where conditional probabilities of the genotypes were also calculated).

With regard to claim 79, Jean-Pierre teaches an embodiment of claim 78, wherein each probability distribution associates a hypothetical pair of first and second reaction values with a single probability of each genotype of interest (p. 328, where conditional probabilities of the genotypes were also calculated).

With regard to claim 85-86, Jean-Pierre teaches an embodiment of claim 75, wherein step (E) further includes the step of calculating a confidence score, associated with the determination of the genotype in step (E), based on data from step (D) (p. 328 and 329, where scores were calculated which associated the genotype with probability).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Nikiforov to use the conditional probability distribution method of Jean-Pierre. JeanPierre motivates the use of computation of unknown genotypes to analyze the conditional probabilities relative to a distribution of hypothetical reaction values (see page 330). Specifically, Jean-Pierre notes, "this paper presents a procedure for deriving the probability of a genotype from the probabilities conditional on the genotype that can be obtained from any risk calculation program. The expression of the risk as a function of the possible genotypes exposes a hazard of misinterpretation" (p. 325). Jean-Pierre also teaches, "Information on genotype is here derived from computer risk estimation: however complex the

computation algorithm is, data can be simply organized so as to make inferences on the unknown genotype" (p. 329). An ordinary practitioner would have been motivated to apply this hypothetical distribution analysis to genotyping since Jean-Pierre notes the gains from creating such a distribution include avoiding hazards such as incorrectly using the simple average of the conditional probabilities instead of the harmonic mean, to more accurately determine the genotype (see page 330). Therefore, one of ordinary skill in the art would have been motivated to modify the method of Nikiforov to use the conditional probability distribution method of Jean-Pierre with a reasonable expectation for success.

Response to Arguments

Applicant's arguments with respect to claims 75-76, 78-82, 85-86, 91-92, 94-95, 116-118 have been considered but are moot in view of the new ground(s) of rejection.

Conclusion

No claims are allowed. All pending claims stand rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STEPHANIE K. MUMMERT whose telephone number is (571)272-8503. The examiner can normally be reached on M-F, 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Stephanie K. Mummert/
Examiner, Art Unit 1637